The Examiner requests Applicants to send the office another set of copies of the references.

Copies of the references listed in the information disclosure statement are submitted along with this response.

3. 35 U.S.C. § 112, first paragraph.

The Examiner rejects Claims 27 and 38 under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Examiner alleges that the antibodies HuZAF, 5F2, 16F2, 16G2, and 20E11 are required to practice the claimed invention, and as a required element, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. Claim 27 is canceled. Applicants respectfully traverse the rejection of Claim 38.

Regarding canceled Claim 27, Applicants point out that HuZAF is an anti-interferon-γ antibody.

As stated in the specification (page 15, lines 26-27), the antibodies 5F2, 16F2, 16G2, and 20E11 are described in Gately, *et al.* (WO 99/37682), which states "the corresponding hybridoma cell line producing these antibodies has been deposited on December 11, 1997 under the conditions of the Budapest Treaty at the American Type Culture Collection under ATCC accession numbers HB-12446, HB-12447, HB-12449, and HB-12448, respectively" (page 13, lines 8-13). U.S. Patent No. 6,225,117 (which corresponds to WO 99/37682) also recites the deposition of antibodies 5F2, 16F2, 16G2, and 20E11 on December 11, 1997 under the conditions of the Budapest Treaty at the American Type Culture Collection under ATCC accession numbers HB-12446, HB-12447, HB-12449, and HB-12448, respectively (col. 8, lines 19-32). Accordingly, these antibodies are readily available to the public upon the granting of this application.

For the reasons stated above, Applicants respectfully request that the Examiner withdraw the rejection of Claims 27 and 38 under 35 U.S.C. §112, first paragraph.

4. 35 U.S.C. § 102(a)

The Examiner rejects Claims 25-26, 33-37, and 39-42 as allegedly being anticipated by WO 98/16248, as evidenced by U.S. Patent No. 5,440,021. Claim 26 is canceled. Applicants respectfully traverse this rejection of Claims 25, 33-37, and 39-42.

MPEP 2121.01 states:

> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an **'enabling disclosure'**... ." *In re Hoeksema,* 399 F.2d 269, 158 USPQ 596 (CCPA 1968). A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985)." (emphasis added).

The court in *Donuhue* stated that:

> "Accordingly, even if the claimed invention is disclosed in a printed publication, that **disclosure will not suffice as prior art if it was not enabling**. *In re Borst*, 345 F.2d 851, 855, 145 USPQ 554, 557 (CCPA), *cert. denied*, 382 U.S. 973, 148 USPQ 771 (1966.)" (226 USPQ at 621; emphasis added).

WO 98/16248 discloses "a method of treating or preventing an autoimmune disease in a subject comprising orally administering to the subject an antigen associated with the autoimmune disease and administering an inhibitor of IL-12 in amounts sufficient to treat or prevent the autoimmune disease" (page 3, lines 20-24). WO 98/16248 discloses that the "antibodies to IL-12, in soluble form would be administered parenterally in a single dosage of between 1 mg and 100 mg/kg of body weight, with a preferred dosage range of 5-50 mg/kg and most preferred dosage of between 10 and 20 mg/kg." (page 9, lines 14-17). WO 98/16248 discloses an experiment whereby OVA-TCR transgenic mice were fed high doses of OVA (250 mg of OVA protein) and injected with 0.75 mg of a rat monoclonal antibody to murine IL-12 (page 12, lines 25-27). The results reported are that, after 96 hours, mice fed OVA and injected with anti-IL-12 antibody had a more rapid and significant decrease in proliferation of Peyer's patches (PP) and mesenteric lymph nodes (MLN) cells (compared to the mice fed OVA and not injected with anti-IL-12 antibody) (page 18,lines 3-7). There is no teaching that this

mouse model is an established model for treating psoriasis.

Applicants respectfully assert that WO 98/16248 is not enabling of a method of treating a patient suffering from psoriasis comprising the step of administering to the patient a pharmaceutical formulation comprising an antibody that binds to IL-12. **WO 98/16248 does not teach that the injection of 0.75 mg of a rat monoclonal anti-murine IL-12 antibody was to treat the mice for psoriasis.** WO 98/16248 does not teach any dosages or means by which to treat psoriasis in patient using an antibody that binds to IL-12. While WO 98/16248 discloses that an example of an autoimmune disease is psoriasis (page 5, lines 13-15); however, psoriasis is merely one example provided among twenty-five. Moreover, WO 98/16248 is administering the anti-IL-12 antibody to merely help enhance the oral tolerance induced by the feeding of the antigen (page 3, lines 6-11). The disclosure of a generalized method of treating or preventing an autoimmune disease in a subject (by orally administering an antigen associated with the autoimmune disease and administering an inhibitor of IL-12), in combination with the listing of psoriasis as one among twenty-five autoimmune diseases, and the experiment that resulted in the decrease in proliferation of PP and MLN cells, does not provide sufficient teaching to one of ordinary skill in the art to combine with his or her own knowledge to practice a method of treating a patient suffering from psoriasis comprising the step of administering to the patient an antibody that binds to IL-12. Therefore, WO 98/16248 does not provide sufficient teaching so that the public is placed in possession of a method of treating a patient suffering from psoriasis comprising the step of administering to the patient a pharmaceutical formulation comprising an antibody that binds to IL-12.

In contrast, the present application teaches the inhibition of psoriasis lesion in mice by injecting the mice with 0.5 mg of anti-IL-12 monoclonal antibody (page 28, line 22 to page 29, line 18) or 1 mg of anti-IL-12 antibody/mouse/dose (page 32, lines 1-2).

Further, WO 98/16248 discloses a method of treatment that requires the administration of <u>two</u> compounds, an antigen associated with the autoimmune disease <u>and</u> an inhibitor of IL-12 (page 3, lines 14-18). As explained earlier, the example provided by WO 98/16248 involves a treatment that requires <u>two</u> compounds: the feeding

of OVA and the injection of anti-IL-12 antibody. This clearly demonstrates that the WO 98/16248 is not enabled for the present claimed method of treating a patient suffering from psoriasis comprising administering to the patient an antibody that binds to IL-12. In contrast, Applicants in Example 2 demonstrate the efficacy of treating a *scid/scid* mice, with transferred $CD4^{+}CD45Rb^{hi}$ cells to induce psoriasis, using an anti-IL-12 antibody alone (page 31,line 32 to page 32, line 29). Untreated mice had a histology score of 2.5 (moderate to severe symptoms) and anti-IL-12 antibody treated mice had a histology score of 0.25 (none to mild symptoms) (see page 20, lines 8-16 and page 32, lines 5-7). Therefore, in contrast to the non-enabling disclosure of WO 98/16248, Applicants clearly enable a method of treating a patient suffering from psoriasis comprising administering to the patient an antibody that binds to IL-12.

In addition, regarding the Examiner's citation of U.S. Patent No. 5,440,021, there is no reasoning or explanation provided to explain why an affinity of monoclonal antibodies to IL-8, which was able to inhibit binding 80% of IL-8 binding, would be relevant and applicable in demonstrating that the anti-IL-12 antibody of WO 98/16248 would be effective in treating psoriasis. The '021 patent neither discloses an antibody that binds to IL-12 nor a method to treat psoriasis.

Therefore, for the reasons stated above, WO 98/16248 is not an enabling disclosure that teaches the method of Claim 25, and thereby WO 98/16248 does not anticipate Claim 25. Neither does WO 98/16248 anticipate the dependent claims of Claims 34-37 and 39-42, which depend from Claim 25.

Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

5. 35 U.S.C. § 103(a)

The Examiner rejects Claims 25-26, 33-37, and 39-42 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,338,848 in view of Menssen, *et al.* (*J. Immunol.*, 15:4078-83 (1995)) and in view of U.S. Patent No. 5,440,021. The Examiner asserts that "it would have been obvious top one of skill who wanted to treat psoriasis to have administered a monoclonal antibody that binds IL-12 to a patient with

psoriasis in according [*sic*] to the method of '848 . . . because '848 teaches that that [*sic*] administering an IL-12 antagonist is effective in treating an autoimmune disease that is promoted by an increase in IFN gamma, and because Menssen et al teach that psoriasis exacerbations can be triggered by systemic administration of IFN gamma" (page 4, lines 29-34). The Examiner also states that the "'848 patent does not teach that psoriasis is an autoimmune disease that is promoted by an increase in levels of INF gamma" (page 4, lines 23-24). Claim 26 is canceled. Applicants respectively traverse this rejection of Claims 25, 33-37, and 39-42.

There is no reasonable expectation of success that administering the anti-IL-12 antibody of the '848 patent would be successful in treating a patient suffering from psoriasis vulgaris as disclosed in Menssen, *et al.*

The '848 patent discloses the administration of sheep polyclonal anti-murine IL-12 antibody to mice induced with experimental allergic encephalomyelitis (EAE) (col. 10, lines 22-50). According to the '848 patent, "EAE is widely recognized as an acceptable animal model for multiple sclerosis in primates" (col. 7, lines 56-57), and EAE induction is done by transferring PLP stimulated LNC to mice (col. 9, lines 52-53).

Menssen, *et al.* disclose that "Psoriasis exacerbations can be triggered by systemic application of the T cell growth factor IL-2 . . . or of IFN-γ or IFN-α . . . ." (page 4078, left column). While the '848 patent discloses that "in vitro stimulation of LNC with PLP resulted in greater than 10 fold increase of IFN-γ . . . and a two fold increase in IFN-α in the cell culture supernatant" (col. 9, lines 32-36), there is no evidence provided to support that EAE is caused by an increase of IFN-γ or IFN-α. The Examiner bases her reasoning on the premise (which Applicants do not agree) that the anti-IL-12 antibody treatment of '848 is suitable for treating any "autoimmune disease that is promoted by an increase in IFN-γ. However, this premise is not established as the '848 patent does not teach that the EAE model utilized demonstrates a causal relationship between an increase of IFN-γ with the triggering of an autoimmune disease. Subsequently, there is no evidence provided to support that a method to treat EAE can be successfully applied to treat any disease caused by an increase of IFN-γ or IFN-α. Therefore there is no motivation or suggestion to combine Menssen, *et al.* with '848 based on the reasoning provided by the Examiner.

In addition, there is no teaching or suggestion that EAE, or "an acceptable animal model for multiple sclerosis in primates", is an acceptable model for psoriasis. Menssen, *et al.* do not provide any teaching or suggestion that the "an acceptable animal model for multiple sclerosis in primates" of the '848 patent is an acceptable model for psoriasis. There is no reasoning or suggestion that a composition able to produce a positive result in EAE, an animal model for multiple sclerosis, is also capable of producing positive results in treating psoriasis. Therefore, there is no reasonable expectation that administering the anti-IL-12 antibody of the '848 patent would be successful in treating a patient suffering from psoriasis vulgaris as disclosed in Menssen, *et al.*

In regards to U.S. Patent No. 5,440,021, as iterated earlier, the '021 patent does not disclose an antibody that binds IL-12, a method to treat psoriasis or provide any support that an antibody that binds IL-12 can be used to treat a patient suffering from psoriasis. The '021 patent does provide any reasoning or suggestion that a composition able to produce an positive result in EAE, an animal model for multiple sclerosis, is also capable of producing positive results in treating psoriasis. Therefore the '021 patent does not cure the deficiency of the '848 patent and Menssen, *et al.*

For the reasons stated above, the cited references do not render Claims 25, 33-37, and 39-42 obvious. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

CONCLUSION

In view of the foregoing amendment and remarks, the Applicants believe that the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 463-8109.

Respectfully submitted,

Dated: August 22, 2003

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